UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,870	03/21/2001	Philip A. Cole	01107.00108	8634

22907 7590 05/18/2005

BANNER & WITCOFF
1001 G STREET N W
SUITE 1100
WASHINGTON, DC 20001

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,870	COLE ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-7,10-13,15,58,60,63,67,69-71,74 and 77-88* is/are pending in the application.

4a) Of the above claim(s) *77-86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-7,10-13,58,60,63,67,69-71,74,87 and 88* is/are rejected.

7)☒ Claim(s) *15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1, 5-7, 10-13, 15, 58, 60, 63, 67, 69-71, 74, and 77-88 are pending in the application.

[2] Applicants' amendment to the claims, filed 2/28/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicants' arguments filed on 2/28/2005 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[4] The text of those sections of Title 35, U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[5] Newly submitted claims 77-86 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons. The elected claims are drawn to a bisubstrate inhibitor of an insulin receptor kinase (IRK) or a protein kinase (PK). Claims 77-86 are drawn to a method of making a candidate bisubstrate inhibitor of an insulin receptor kinase (IRK) or a protein kinase (PK). MPEP § 806.05(f) states that inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and

materially different process (MPEP § 806.05(f)). In the instant case, the inventions are distinct as the compounds made by the methods of claims 77-86 encompass compounds that are not necessarily bisubstrate inhibitors of IRK or PK. For example, the methods require bromoacetylating an amine group to form a bromide group and it is not clear as to whether the amine group that is bromoacetylated is the free amino group at the N-terminus of the peptide, or the amino group resulting from reducing the nitro group. As such, the compounds that are synthesized are not necessarily the claimed compounds.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 77-86 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. See also MPEP § 821.04 regarding rejoinder of process claims.

[6] Claims 1, 5-7, 10-13, 15, 58, 60, 63, 67, 69-71, 74, and 87-88 are being examined on the merits.

[7] Applicants' arguments filed 2/28/2005 are acknowledged. Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[8] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objection

[9] While the structure of "Compound 2" is definite (see comments below addressing the withdrawal of the rejection of claim 15 under 35 U.S.C. 112, second paragraph), claim 15 is objected to as the structure of "Compound 2" is not present in the claim. It is suggested that, for example, applicants incorporate the structure of "Compound 2" as shown in Figure 1A into the claim.

Claim Rejections - 35 USC § 112, Second Paragraph

[10] The rejection of claims 1 (claims 4-14 and 58 rejected as being dependent therefrom) and 60 (claims 63, 66-67, and 69-76 rejected as being dependent therefrom) (¶ [6] part [a] of the Office action mailed 10/28/2004) is withdrawn in view of the amendment to the claims. The nucleotide analog moiety of claims 1 and 60 has been limited to γ-S-ATP. It is noted that the specification fails to disclose a "γ-S-ATP" nucleotide analog moiety. However, the specification discloses an "ATPγS" or an "ATPγ-S" nucleotide analog moiety throughout the specification (see, e.g., pp. 5 and 7). In the interest of advancing prosecution, the examiner has interpreted "γ-S-ATP" as being identical to "ATPγ-S." If this interpretation is incorrect, applicants should so state and clarify the record.

[11] The rejection of claim 15 (¶ [6] part [c] of the Office action mailed 10/28/2004) as being unclear in the recitation of "Compound 2" is withdrawn in view of applicants' clarification of the term. Applicants state for the record that Compound 2 is shown in Figure 1A denoted with the numeral "2."

[12] The rejection of claims 69-71 and 74 as being indefinite in the recitation of "natural substrate" (¶ [6] part [d] of the Office action mailed 10/28/2004) is maintained for the reasons of record and the reasons stated below.

RESPONSE TO ARGUMENT: At the top of p. 12 of the response, applicants argue the term "natural substrate" is to mean "a physiological substrate found in the same cells as the protein kinase" and that "[t]he natural substrate or physiological substrate is a protein." Applicants note the term "unnatural substrate" is not used in the claims.

Applicants' argument is not found persuasive. The peptide moiety of the PK inhibitor of claim 60 is described as "a substrate for said protein kinase and which comprises a 2-amino-3-(4-amino-phenyl)-propionic acid residue or a 2,3-diamino-propionic acid residue." The examiner has interpreted this term as meaning a PK peptide substrate having the amino acid that is targeted for phosphorylation replaced with either of a 2-amino-3-(4-amino-phenyl)-propionic acid residue or a 2,3-diamino-propionic acid residue. The examiner maintains that the scope of those peptide or protein moieties that are "natural" PK substrates is unclear. While applicants state that the term "natural substrate" is meant to be interpreted as "a physiological substrate found in the same cells as the protein kinase," this definition fails to clarify the scope of intended peptide or protein moieties. For example, if one were to recombinantly express an "unnatural" peptide or protein in a mammalian cell line and a PK phosphorylated that "unnatural" peptide or protein, would it still be considered a "natural" PK substrate? It remains unclear to the examiner as to how a skilled artisan distinguishes a "natural" PK

substrate from an "unnatural" PK substrate and it is suggested that applicants further clarify the meaning of the term. The examiner acknowledges that the term "unnatural" does not appear in the claims. This term was used by the examiner to describe those peptides that would not be encompassed by the term "natural substrate." It is noted that even applicants make such a distinction in the instant response (see, e.g., p. 16, bottom).

[13] The rejection of claims 1-14, 58, 60, 63, 66-67, 69-71, and 74-76 as being indefinite in the recitation of "the tether is greater than or equal to 4.9 Å measured from a gamma phosphorous of the nucleotide or nucleotide analog moiety to a proton donor" (¶ [7] of the Office action mailed 10/28/2004) is withdrawn in view of the amendment to the claims. The tether has been limited to an acetamide.

Claim Rejections - 35 USC § 112, First Paragraph

[14] The written description rejection of claims 1, 5-7, 10-13, 58, 60, 63, 67, 69-71, 74, and 87-88 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record (¶ [8] of the Office action mailed 10/28/2004) and for the reasons stated below.

RESPONSE TO ARGUMENT: Beginning at the middle of p. 13 of the response, applicants address written description of the nucleotide analog moiety and the tether. Applicants argue "[t]he claims have been amended so that a particular nucleotide analog moiety and a particular tether are recited" and that "each of these elements of the claims are fully and adequately described."

The examiner acknowledges that the nucleotide analog moiety and tether have been limited to specific structures, which are adequately described in the specification.

Regarding the peptide moiety, applicants argue that numerous sequence motifs of substrates for IRKs and other PKs are known in the prior art, citing references already of record. According to applicants, in view of the prior art, a correlation between structure and function of peptide substrates of protein kinases generically and of IRK in particular is known. Applicants further argue that numerous peptide substrates of IRK and other PKs were known in the prior art, and according to applicants, "it is clear that the applicants were in possession of them." Applicants argue that it is not necessary for a specification to disclose the sequences of peptide substrates of IRKs and other PKs that were known in the prior art at the time of the invention. Applicants argue these prior art-recognized species of peptides are representative of the entire genus of peptide moieties. Applicants submit that "the genus of peptides is amply known in the art and that the PTO does not need to have further demonstration that this is the case."

Applicants' argument is not found persuasive. The examiner acknowledges that specific sequences and generic sequence motifs of substrates for IRKs and other PKs were known in the art at the time of the invention. While the examiner acknowledges these representative species, the examiner maintains the position that these representative species fail to describe the genus of substrates of IRKs and other PKs, which encompasses any IRK or PK substrate peptide sequence, including full-length polypeptides that have yet to be isolated. In this case, using claims 1, 60, and 87-88 as examples, the peptide moieties are described by a single, sole structural feature, i.e.,

that the peptide comprises "a 2-amino-3-(4-amino-phenyl)-propionic acid" or a "2,3-diamino-propionic acid residue." The remaining structure of the peptide moiety, which can be of any length/size, including full-length polypeptides that have yet to be identified, is completely undefined. Consequently, the genus encompasses species that are widely variant with respect to the structure of the recited peptide moiety. While it is acknowledged that the recited structural feature, including the additional structural features of claims 5-7 is/are common to all members of the genus of peptide moieties, this feature fails to constitute a substantial portion of the genus of peptide moieties.

It is noted that applicants have failed to address the examiner's remarks specifically regarding claims 58, 67, 69-71, and 74. See ¶ [8], p. 7, of the Office action mailed 10/28/2004. Thus, for the record it would appear that applicants do not dispute the examiner's assertions based on these remarks.

[15] The scope of enablement rejection of claims 1, 5-7, 10-13, 58, 60, 63, 67, 69-71, 74, and 87-88 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record (¶ [9] of the Office action mailed 10/28/2004) and for the reasons stated below.

RESPONSE TO ARGUMENT: The examiner will address the Factors of In re Wands in the order listed by applicants in their response.

The Breadth of the Claims: Applicants assert the claims have been amended such that the only element which is not specified structurally is the identity of the peptide moiety.

The examiner agrees with applicants' assertion. The nucleotide analog and the tether of the claimed inhibitors have been limited to specific structures. Regarding the

peptide moiety, claims 1 and 60 are so broad as to encompass any peptide moiety that is an IRK or PK substrate with the target of amino acid phosphorylation replaced with a 2-amino-3-(4-amino-phenyl)-propionic acid or a 2,3-diamino-propionic acid residue. The peptide moiety of claims 87-88 is so broad as to encompass any peptide moiety comprising a 2-amino-3-(4-amino-phenyl)-propionic acid or a 2,3-diamino-propionic acid residue. It is noted that the peptide moiety is unlimited with regard to size and encompasses full-length proteins, including proteins that have yet to be described. While the remaining claims are further limiting, these claims still encompass a vast number of peptide sequences, including, as noted above, full-length proteins. It is also noted that claims 60 and 88 broadly encompass an inhibitor of any PK, including protein kinases whose substrates have yet to be determined.

The State of the Prior Art: Applicants assert the state of the prior art was advanced at the time of the invention with regard to the components for making the claimed inhibitors. Applicants argue "[a] host" of peptide substrates, both natural and non-natural, were known in the prior art, including 19 IRK peptide substrates and 82 PK substrates identified in prior responses. According to applicants, a skilled artisan would only need to select from those peptides that are known in the art.

Applicants' argument is not found persuasive. There is no dispute that several IRK and PK peptide substrates were known in the prior art at the time of the invention. As previously noted, the recited peptide moiety is not limited to those IRK or PK peptide inhibitors or generic, motif-based consensus sequences known in the prior art at the time of the invention. In this case, the peptide moiety goes beyond those peptides,

including full-length proteins, that were known in the art at the time of the invention and encompasses those that have been isolated after the time of the invention, and even those that have yet to be isolated.

The Skill in the Art: Applicants argue the level of skill in the art was high at the time of the invention and that a skilled artisan would have a Ph.D. plus post-doctoral experience. Applicants argue such a skilled artisan would have knowledge of art-disclosed peptide substrates or be able to find them using simple automated literature searches.

Applicants' argument is not found persuasive. The examiner agrees that the level of skill in the art of chemical synthesis was high at the time of the invention. However, while a skilled artisan may have had knowledge or access to knowledge of art-recognized peptide substrates, a skilled artisan would have had no way to predict those IRK and other PK peptide moiety substrates that were not known in the art at the time of the invention. In this case, the claims are not limited to those peptide substrates that were "art-recognized" at the time of the invention. In this case, the peptide moiety goes beyond those peptides, including full-length proteins, that were known in the art at the time of the invention and encompasses those that have been isolated after the time of the invention, and even those that have yet to be isolated.

Level of Predictability: Applicants argue that, in view of the prior art and skill in the art at the time of the invention, the predictability for making the claimed compounds would also be high. Applicants argue the PTO has set forth no reasons why the elements of the claimed compounds could not have been predictably joined. Applicants

argue the Cole Declaration presents 5 additional working examples of functional inhibitors and that such "actual evidence of success rebuts mere speculation that the invention *may* not work" (emphasis in original).

Applicants' argument is not found persuasive. There is no dispute that one of skill in the art, after having isolated/made all peptide moieties as broadly encompassed by the claims, could assemble the elements of the compound. However, it is the examiner's position that it would require undue experimentation for a skilled artisan to isolate/make all peptide moieties as encompassed by the claims. While the prior art teaches IRK and other PK peptide substrates, including full-length polypeptides, there is no way to predict a priori all polypeptide moieties that can serve as substrates for any IRK or any PK based on the state of the art at the time of the invention. It is noted that the specification provides only two working examples of the claimed inhibitors, i.e., compounds 2 and 4. The peptide moieties of compounds 2 and 4 are less than 20 amino acids in length and the specification provides no guidance or working example such that a skilled artisan would have an expectation that full-length polypeptides or peptides of lengths greater than those of compounds 2 and 4 would be useful as bisubstrate inhibitors as one of skill in the art would reasonably expect that, due to steric effects, such full-length polypeptides or peptides of lengths greater than those of compounds 2 and 4 may interfere with binding to the cognate IRK or PK.

Regarding the Cole Declaration, as noted in a previous Office action, it is not clear as to whether the peptide moieties of the 5 additional working examples shown in the Cole Declaration were known to a skilled artisan at the time of the invention. Even

assuming arguendo the peptide moieties of the 5 additional working examples of the Cole Declaration were known to a skilled artisan at the time of the invention, as noted in a previous Office action, the peptides denoted as D. and E. in the Cole Declaration do not meet the limitations of the peptide moiety of the claimed inhibitors as these peptide moieties do not have the required amino acid as recited in the claims.

Quantity of Experimentation: Applicants argue all components of the claimed inhibitor compounds were known at the time of the invention, a skilled artisan merely need assemble these component parts, and such assembly would require only routine experimentation and would not require extensive or undue experimentation.

Applicants' argument is not found persuasive. The examiner maintains the position that undue experimentation is required to make the full scope of claimed inhibitor compounds. There is no dispute that the nucleotide analog and the tether components of the inhibitor compound were known in the art at the time of the invention. However, the broad scope of peptide moieties as encompassed by the claims was not known at the time of the invention. Thus, a skilled artisan must first isolate/make all peptide moieties as encompassed by the claims, which, in view of the broad scope of the claims and the high level of unpredictability (as discussed in detail above) and the lack of guidance and working examples (as discussed in detail in previous Office actions), would have required undue experimentation.

Conclusion

[16] Status of the claims:

- Claims 1, 5-7, 10-13, 15, 58, 60, 63, 67, 69-71, 74, and 77-88 are pending.
- Claims 77-86 are withdrawn from consideration.
- Claim 15 is objected to for the reason(s) presented above, but otherwise appears to be in a condition for allowance.
- Claims 1, 5-7, 10-13, 58, 60, 63, 67, 69-71, 74, and 87-88 are rejected.
- No claim is in condition for allowance.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Thursday and alternate Fridays from 6:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (571) 273-8300. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVID J. STEADMAN, PH.D.
PRIMARY EXAMINER